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Cognitive retraining and functional treatment (CRAFT) for adults with cancer related cognitive impairment: A randomized controlled trial

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Abstract

Purpose: To examine the applicability and efficacy of Cognitive Retraining and Functional Treatment (CRAFT) combining remote computerized cognitive training (CCT) and occupation-based treatment in adults with cancer-related cognitive impairment (CRCI).

Methods: Three-armed randomized controlled trial including 74 individuals with CRCI, randomized into 12 weeks of either CRAFT, CCT alone, or treatment-as-usual. Assessments evaluating participation in daily life, perceived cognition, cognitive performance, quality-of-life, and treatment satisfaction were administered at baseline, post-intervention and 3-month follow up.

Results: Significant time X group interactions in favor of the CRAFT and CCT groups were found for participation in daily life (F2,34=5.31, p=.01, eta=.238), perceived cognition (F2,34=4.897, p=.014, eta=.224) and cognitive performance on speed of processing test (F=5.678, p=.009, eta=.289). CRAFT group demonstrated significantly larger clinically meaningful gains on participation in daily life (Chi-square= 6.91, p=.032) and significantly higher treatment satisfaction. All treatment gains were maintained at a 3-month follow-up (n=32).

Conclusions: CCT and CRAFT were found to have a positive impact on participation and cognitive outcomes among individuals with CRCI. The CRAFT showed an additional advantage in improving self-chosen occupation-based goals suggesting that a combination of cognitive training with occupation-based intervention has a positive synergistic effect resulting in 'real world' health benefits.

Implications for Cancer Survivors: A combination of cognitive training with occupation-based intervention has a positive effect resulting in clinically meaningful improvements in participation in daily life, objective cognitive performance, and subjective cognitive impairment.

Clinical Trial Registration: ClinicalTrials.gov NCT04210778, December 26, 2019, retrospectively registered.

Introduction

Up to 75% of long-term cancer survivors report having mild to moderate cognitive impairment known as cancer related cognitive impairment (CRCI). It is unclear what causes CRCI, and it seems to be related to the cancer itself, treatments associated with cancer, as well as to psychological factors such as mood. CRCI primarily involves deficits in memory, attention, executive functioning, language, and speed of processing [1, 2]. Moreover, challenges and deficits in functional cognition are evident, impeding survivors' participation in daily life. *Functional cognition* combines the constructs of cognition with function and hence refers to a one's ability to implement cognition in his/her real-life scenarios. This ability is affected not only by cognitive skills but also by the interplay of personal factors, activity demands and environmental affordances [3, 4]. Occupations that seem to be affected among individuals with CRCI are instrumental activities of daily living (such as shopping and medication management), physically demanding leisure activities (such as camping and sports), sedentary leisure activities (such as reading), social activities (such as visiting friends) [5], and work [6]. Despite the negative effect of CRCI on survivors' daily life, the best option for non-pharmacological treatment remains unknown [7].

Computerized cognitive training (CCT) is a bottom-up intervention based on neuroplasticity and is aimed at improving specific cognitive functions by repeatedly practicing graded tasks adapted to the individual's performance [8]. The application of CCT has shown some promise as a non-pharmacological intervention for CRCI [2, 7]. Two recent reviews concluded thatthe majority of studies found intervention effects on cognitive performance tests and subjective perception of cognitive functioning, and fewer studies report changes in participation in daily activities quality of life [9, 10]In addition, more evidence is needed to determine the sustainability of treatment gains [11]

In contrast to CCT, which addresses the underlying cognitive deficits, treatments of functional cognition problems are directed to the unique participation challenges, using top-down, goal directed, occupation-based approaches [12]. The cognitive orientation to daily occupation approach (CO-OP Approach) is a widely studied treatment directed at improving participation in activities

relevant to the client [3, 13]. By using a global meta cognitive strategy 'goal-plan-do-check', clients set functional goals, create, and carry out action plans and monitor their performance. Evidence from studies assessing the CO-OP show that participants improve on goals directly addressed during treatment as well as on novel and untrained goals [14–16].

Here, we examine the applicability and efficacy of a novel intervention, the cognitive retraining and functional treatment (CRAFT). CRAFT harnesses the potential integrative power of both top-down (CO-OP) and bottom-up (CCT) methods, and may therefore help cancer survivors cope with both their cognitive deficits *and* their implications in daily life [17]. Moreover, the CRAFT intervention has been designed to be applied within a telerehabilitation framework. Cancer survivors are particularly suitable candidates for remote treatment as they are generally coping with long-term cancer repercussions (such as pain and fatigue), may not be keen on additional clinic visits, and are likely to have sufficient technological experience [18–20]. The feasibility, acceptability, and preliminary efficacy of the CRAFT intervention have been established in a small-scale pilot study which was recently completed [21]. These encouraging preliminary results warranted the need for a larger scale study. Therefore, the aim of the current study was to examine the efficacy of CRAFT for adult cancer survivors with CRCI in a three-armed randomized control trial (RCT), comparing 12 weeks of CRAFT, CCT and Treatment as usual (TAU). We hypothesized that: 1. The CRAFT group would show larger gains in participation in daily life compared with the other two groups; 2. Both CRAFT and CCT would be applicable and participants will show similar gains in cognitive measures and in QoL following intervention, and higher than those of the TAU group; 3. Participants in the CRAFT and CCT groups will report high treatment satisfaction. 4. Gains made following the intervention period would be maintained following 3 months of no-contact period.

Materials And Methods

Design:

This was a 3 arm (CRAFT; CCT; TAU) X 2 time points (baseline; post- intervention) randomized controlled trial (RCT), with an exploratory 3 month follow up. The study was approved by the Hadassah Helsinki ethics committee (0138-18-HMO). An a priori power analysis using G* Power version 3.1.7, for a one-way ANOVA with 3 groups, an alpha of 0.05, a power of 0.80, and an assumption of 0.5 effect size, based on our pilot study, yielded a desired sample size of 66 subjects. With an estimated drop-out rate of 20% we aimed to recruit a sample of 81 participants (27 in each group). The recruitment of this study took place between June 2019 to March 2022 and was therefore interrupted by the COVID-19 pandemic, resulting in a smaller-than-planned sample size.

Participants and procedure

All participants were recruited from the Hadassah medical center in Jerusalem, Israel,. Patients who voiced complaints regarding their cognitive state during clinic appointments were referred by their oncologist to the study's research assistant (RA) for information about the study. Initial eligibility for the study was established through a short phone interview with the RA. Eligibility criteria were: (1) A previous diagnosis of an adult-onset non-central nervous system (CNS) cancer; (2) Completion of active cancer treatment at least 6 months prior to enrollment; (3) Age: 18–75 years old; (4) Expressed subjective concerns about cognitive decline due to cancer diagnosis or treatment. This was obtained by providing the answer 'yes' to the question: 'do you have concerns about your memory or other thinking abilities following cancer or cancer treatment?' and (5) Daily access to a computer and internet facilities and basic computer literacy. Exclusion criteria were: (1) A history of a central nervous system tumor or other severe neurological disorders; (2)unstable psychiatric condition (according medical file) (3) major cognitive decline (MOCA < 19 [22]).

Assessments were administered at 3 time points: at baseline (T0), immediately after the intervention or after 12 weeks (T1) and after a 3 month no-contact follow up (T2). Each assessment appointment lasted between 60–90 minutes and was administered by an occupational therapist. The first assessment was administered in person, either in the hospital or in the participant's home (depending on their choice) and included signing an informed consent. However, due to the COVID-19 pandemic, participants were offered the choice of using Zoom for their post-intervention and follow up assessments. An outcome assessor who was blinded to participants' group assignment administered the post- intervention assessment.

At completion of the baseline assessment participants were randomly assigned to one of the three study arms: CRAFT, CCT, TAU, by means of minimization using the WINPEPI computer program. The groups were balanced for initial cognitive status (Montreal cognitive assessment; MOCA < 26 versus MOCA ≥ 26) [22], and for time since last treatment (less vs. more than 5 years) [23]. Participants who completed all study procedures received a compensation of approximately 100$.

Interventions

The CRAFT protocol included approximately 12 weeks of remote intervention comprised of a weekly CO-OP meeting (1hr) and three weekly sessions (25min each) of CCT. The CO-OP sessions were administered remotely via Zoom. Three occupational therapist's (OT's) trained in the CO-OP Approach™ [24] delivered the intervention. All CO-OP sessions were described in detail in a written therapist log. After each session, the research coordinator read over the therapist log and discussed the details of the treatment to ensure treatment fidelity. The CCT was performed independently on participants' personal computers. Minimal adherence required for inclusion in the statistical analysis was participating in at least 8 CO-OP sessions and completing at least 3 hours of CCT over the course intervention period.

The CO-OP Approach™ was originally developed for children with developmental coordination disorder and was adapted over the years to multiple populations including adults with cognitive decline and cancer survivors [25, 26]. Building on these previous adaptations and conclusions from CRAFT pilot study, the following protocol was administered: Unit 1 (meetings 1 + 2) included initial information regarding the CO-OP Approach ^{TM} and an introduction to the global problem-solving strategy - "Goal-Plan-Do-Check"; A psychoeducation session including explanation regarding CRCI, cognitive domains that may be affected and participation restrictions often reported; and choosing the first goal to target (from the goals defined using the COPM). Unit 2 (meeting 3 onwards) included working towards achieving goals by using the global strategy: setting a *goal*, coming up with a *plan* to achieve the goal, *doing* the plan in between sessions and *checking* if plan worked in the following session. By learning to analyze their performance, participants were encouraged by the OT to self-discover strategies within an occupational context [27]. Unit 3 (last session or two) was aimed at summing up the process and promoting transfer and generalization of acquired strategies to distally related contexts.

The CCT component included five cognitive training exercises aimed at improving the cognitive abilities of attention, speed of processing, visual working memory and attentional control. Training exercises were taken from Posit Sciences' BrainHQ suite, which was translated to Hebrew by the study staff (see supplementary file 1). Training difficulty level is automatically adjusted to provide a success rate of about 80% for each block in a task, assuring that training was kept within the appropriate challenge level throughout the intervention period. During each weekly meeting the OT checked in with the participant regarding the CCT to troubleshoot any problem, hear feedback and facilitate connection between cognitive training and activities of daily living. Participants assigned to the CCT arm were instructed to complete three weekly sessions (25min each) of training, including the five exercises as mentioned above. In addition, they received a weekly check-in phone call by an occupational therapist to remind them to complete sessions and troubleshoot any issues. Data regarding practice time was obtained through the BrainHQ researcher portal.

The TAU group were a no – contact control and discharged with no further therapy as part of the study. At completion of all study procedures, they were offered access to the CCT.

Outcome Measures

Sociodemographic and clinical characteristics. Sociodemographic data was collected using a background questionnaire and included information regarding age, gender, living and marital status, education, and employment status. Medical information including cancer type, time since treatment completion and treatment modalities were collected from medical documentation by the RA. In addition, the MOCA was administered in order to screen for dementia. Due to the high prevalence of depressive symptomatology in this population and its known impact on cognition [28] this variable was evaluated using the Patient health questionnaire (PHQ-9) [29] and controlled for in the analysis.

All outcome measures were administered in Hebrew using validated translated questionnaires.

Primary outcome

Participation in everyday life. The Canadian Occupational Performance Measure (COPM) [30] is a semi-structured interview aimed at assessing clients self-perception of participation in everyday life. The COPM has been found to be reliable, valid and responsive and has been used with adult cancer survivors [31, 32]. During the interview, clients identify five most important occupational problems. Each problem is then framed as a participation goal and rated on a 10-point scales of performance and satisfaction (1 = not able to do it/ not satisfied at all, 10 = able to do it extremely well/ extremely satisfied). *Trained goal*s refer to three out of the five identified problems that are used as the goals of the CO–OP treatment among participants receiving the CRAFT treatment. *Untrained goals* refer to two (or more) of the occupational problems that are not addressed during treatment. Untrained goals in the CRAFT group can be conceptualized as transfer goals, as they allow to assess the change in participation that are not treated directly. For comparison between groups, untrained goals were used for the CRAFT group since CCT, and TAU have untrained goals only.

Secondary outcomes

Perceived cognitive function. The Functional Assessment of Cancer Therapy – Cognition (FACTcog) [33] is a self-report questionnaire assessing memory, concentration, language and thinking abilities among people with CRCI. The questionnaire includes 37-items rated regarding the past 7 days. The total score ranges from 0 to 148, with higher scores indicating better perceived cognitive function. Items are grouped into 4 subscales: perceived cognitive impairment (PCI), perceived cognitive abilities (PCA), comments from others (OTH), and impact on quality of life (QoL). Having acceptable reliability and validity, this measure has been widely used in cancer populations [34, 35]. In the current study internal consistency was found to be excellent (Cronbach's alpha = 0.909).

Cognitive performance. We used 3 computerized assessments from the BrainHQ by Posit Science Inc. suite (www.brainhq.com), with tests a and b also used as a practice tasks described abovie. The tests were administered using the lab laptops. Participants completed a trial test before completing each assessment. The final scores of the tests are reported in Z-scores by Posit Science Inc.

(a) Bubble pop (Moving objects tracking; MOT): users are instructed to follow dots as they move on the screen for 6 seconds, while ignoring distractors (other dots that also move on the screen at the same time). This test measures visual -spatial working memory abilities and attentional control. The outcome reported is the average number of dots that were successfully tracked.
(b) Double decision (Useful field of view; UFOV): users must simultaneously detect a target in the center of the screen (either a car or a truck) and target in the periphery (Route 66 sign). This test assesses the size of the participant's useful field of view, which is also described as speed of processing (SOP). The outcome reported is a threshold for 75% success in the task is presented in milliseconds.
(c) Sound sweeps: users are asked to identify the direction of tonal change in a sequence of two successive frequency-modulated sound sweeps. This test assesses auditory SOP. The outcome reported is measured as $\log_{10}$(average reaction time in seconds).
Quality of Life (QoL). The Functional Assessment of Cancer Therapy - General practice (FACT-GP) [36] is a self-report questionnaire commonly used to assess QoL in cancer survivors engaged in clinical research. The respondent is asked to consider the last week and rate 21 statements on a 5-point scale based on how much he or she agrees with them. The statements are grouped into four domains (physical, social, emotional, and functional well-being) with individual scoring and a total score, higher scores indicating better perceived QOL. The tool has satisfactory psychometric properties [36–39]. In this study, internal consistency was found to be excellent (Cronbach's alpha = .906).

Treatment satisfaction. A satisfaction questionnaire was developed for the use of this study. For the CRAFT group the questionnaire was comprised of 13 questions addressing general satisfaction, satisfaction from the treatment components, from the remote administration, the therapist, and impact of the intervention on daily life. The same questionnaire was administered to the CCT group, omitting 2 questions regarding the CO-OP intervention. Items were scored on a 5-point scale, higher scores indicating higher satisfaction. In our sample excellent internal consistency was found (Cronbach's alpha = .900).

Data analysis

Data was analyzed using SPSS software. Descriptive statistics are expressed as mean ± SD and used to describe demographic and clinical characteristics of subjects in the three groups. The Kolmogorov-Smirnov test was used to test the normal distribution of the data ($P > 0.05$). Between-group differences at baseline were examined using either chi-square tests or analysis of variance. Hypotheses were tested with mixed model repeated measures (baseline, post-intervention) by group (3 study arms) analysis of variance with post-hoc Bonferroni pairwise comparison. Due to a significant difference in PHQ-9 scores at baseline, this variable was added as a covariate to all analyses. The same model was applied to examine changes between post-intervention and follow up. Effect sizes are reported using partial eta square (η^2). An additional comparison between groups was conducted on the frequency of COPM clinically meaningful change scores (≥ 2 points) [40] using chi-square test. Finally, treatment satisfaction scores were compared between groups using MANOVA. Due to a large proportion of missing data (> 40%) and different drop-out rates between groups [41], missing data was not completed and only data from participants completing both assessments and adhering to treatment protocol was analyzed in the primary analysis.

Results

Applicability

Figure 1 depicts participants flow through the study. From 130 people referred to the study, 74 (57%) passed screening and were randomized to one of the three study arms. Overall, 50 participants (67.5%) completed post-intervention assessment (80% in CRAFT, 64% in the CCT and 58.3% in TAU). No significant differences were found between study completers and non-completers in all groups on demographic and clinical variables (p>.05). Participants in the CRAFT group completed between 8 to 15 CO-OP sessions with an average of 10.3±2 sessions and trained on the BrainHQ program an average of 4.3 ± 3.88 hours over the course of the intervention (range: 0-13.33 hrs). Participants in the CCT group trained on the BrainHQ program an average of 5.08 ±5.07 minutes (range: 0-14.00 hrs). Training time was not significantly different between the groups (p>.05). Within the two intervention groups, 24 participants met full adherence criteria according to their assigned study arm (CRAFT: 70%, n=14; CCT: 62.5%, n=10). The main reasons for non-adherence to CCT requirements in both intervention groups, were time constraints or disinterest in the training. No significant differences were found between participants who fully (n=24) or partially (n=12) adhered to intervention protocol on demographic and clinical variables (p>.05). We observed no adverse events (AEs) associated with the experimental or control conditions. A total of 32 participants from the three study arms participated in the 3-month follow-up.

<insert figure 1 about here>

Table 1 provides demographic and clinical information by group. The mean age across the entire sample was 51.36±10.65 (range :23-73). Most participants were women (75%), married (78%) and had had breast cancer (54%). Other cancer types included 18 types of non-CNS cancers such as colorectal, lung, ovary, and more. The time since treatment completion ranged between 6 months to 11 years with an average of about 3 years. The majority (80%) of the participants were 5 years or less following the last active treatment. However, there were few participants who were more far removed from treatment but still attributed the cognitive complaints to the cancer. ANOVA results comparing the 3 study arms revealed no significant differences between the groups in all demographic and clinical variables; However, participants in the CRAFT group had significantly depressive symptoms (PHQ-9) compared to the other two groups.

<Insert table 1 about here>

Hypothesis 1: Effect of the interventions on participation in daily life

Following the Kolmogorov-Smirnov test, indicating normal distribution of the data (all $P > 0.05$), we examined the immediate effect of the interventions on the primary outcome, i.e., change in the COPM performance and satisfaction of untrained goals. There was a significant time X group interaction effect ($F_{2,34}=5.31$, p=.01, eta=.238) on the COPM performance scale. Post-hoc analysis revealed significant differences between baseline and post-intervention scores for the CRAFT group (p=.000) and for

the CCT group (p=.030), but not for the TAU group (p=.665). Similarly, a significant time X group interaction effect was found on the COPM satisfaction scale ($F_{2,34}$=6.34, p=.005, eta=.272). Post-hoc analysis revealed significant differences between baseline and post-intervention scores for the CRAFT (p=.000) and for the CCT (p=.001) groups, but not for the TAU group (p=.330; see table 2).

We next examined how many participants in each group achieved the criterion for clinically meaningful change for the COPM (≥2 points). Our results showed that the percentages of participants achieving clinically significant change scores on the performance scale (70% CRAFT, 30% CCT, 20% TAU) was significantly higher for the CRAFT group (Chi-square= 6.91, p=.032) compared to the two other groups. For the satisfaction scale, the percentage for CRAFT, CCT, TAU was 79%, 40% and 40% respectively (Chi-square= 5.37, p=.068).

Hypothesis 2: Effect of the interventions on secondary outcomes - self-reported and performance-based cognitive assessments and QoL.

We examined differences between the 3 groups on outcomes related to cognitive performance. We found a significant time X group effect for the FACTcog scale ($F_{2,34}$=4.897, p=.014, eta=.224). Post-hoc analysis revealed significant differences (p<0.05) between baseline and post-intervention scores for all groups. However, the mean change in both CRAFT (change score =22.8±3.85) and CCT (change score = 25.4± 4.35) groups was more than double than the mean change in the TAU group (change score = 8.7 ±3.85) (see Table 3). Related to the performance-based cognitive tasks, we found a significant time X group interaction on the visual SOP task, which was trained directly ("double decision"; F=5.678, p=.009, eta=.289). Post-hoc analysis revealed significant differences between baseline and post-intervention scores for the CRAFT (p=.002) and for the CCT (p=.000) groups, but not for the TAU group (p=.392).. No significant time X group interaction effects were found for two other cognitive assessments, examining attentional control ("Bubble Pop") and auditory SOP ("Sound Sweeps"), the first trained directly and second was not. Finally, no significant time X group interaction was found for QoL (the FACT-GP total and subscales scores; see table 3).

<Insert table 2 about here>

Hypothesis 3: Treatment Satisfaction.

We next compared satisfaction with the intervention applied in the two active groups, receiving CRAFT and CCT, using MANOVA. The analyses revealed that the CRAFT group had significantly higher levels of satisfaction from the intervention compared with the CCT group (CRAFT Total mean 4.32±.38; CCT total mean 3.80±.69; p=.006). Examining each item separately, a significant difference in favor of the CRAFT group was noted on the domains of (a) overall satisfaction ("In general, how satisfied are you with the treatment program you have received"), (b) relevance of treatment to daily problems ("To what extent did the treatment address daily problems"), (c) association between cognition change and daily performance ("To what extent do you feel a change in the influence of your cognitive performance on your daily life"), and (d) handling of cognitive decline ("To what extent do you feel like you handle your perceived cognitive decline better") (all p<.05). Among the CRAFT group, participants were most satisfied with the CO-OP treatment (mean: 4.8±.52) and least satisfied with the CCT (mean: 3.6±1.19). Among the CCT group, participants were most satisfied with the fact the treatment was administered remotely (mean: 4.40±.63), and least satisfied with the extent that the treatment achievements may affect other situations in their life (mean: 2.93±.96; see supplementary file 2).

Hypothesis 4: Longer-term effects of treatment

Follow up assessments were available for only 84% of participants (N=32) (CRAFT -12; CCT-10; TAU-10). Analyses on this sub-group of participants revealed no significant differences between post-intervention outcomes and the 3-month follow-up on all outcome measures (all p>.05) in all three groups. (see table 3 for data comparing post intervention and follow-up outcomes).

<insert table 3 about here>

Discussion

The current 3-group RCT aimed to assess the efficacy of a novel intervention - CRAFT – which combined remotely-applied CO-OP with CCT, compared to the well-studied CCT treatment alone and to TAU. Participants in both intervention groups (CRAFT and CCT) showed significant improvements on participation in daily life and on self-reported and performance-based cognitive outcomes, compared to the TAU group. In addition, the CRAFT participants demonstrated significantly larger *clinically* meaningful gains on participation in daily life, indicating "real world" health benefits, in comparison to both other groups, as well as higher treatment satisfaction. No changes were found across all groups in QoL, and treatment gains were maintained at a 3-month follow-up.

Both treatment groups significantly improved on chosen participation goals, identified using the COPM at the baseline assessment, that were not directly addressed during the intervention. The improvement of the CRAFT group in untrained goals was similar to that found in CO-OP studies among other adult populations as reported in recent reviews [14, 43], yet has not been reported before, to the best of our knowledge, for adults with CRCI [25]. The significant improvement in participation found within the CCT group is notable. Most studies that applied CCT amongst the CRCI population demonstrated relatively proximal transfer of treatment benefits, such as transfer to objective and subjective cognitive performance [44, 45]. Far transfer effects from cognitive training to participation in daily life and QoL were rarely assessed in the CRCI population. [11]. The positive impact of CCT on life goals found in this study is in line with a recently published preliminary study [11] and treatment recommendations for adults with CRCI [46] and adds to the body of research indicating far transfer. This transfer effect may be attributed to both improved speed of processing and/or to a meta cognitive effect, whereby the experience of the cognitive training raised awareness to cognitive functioning and its impact on daily life, leading to active problem solving in daily life [47].

In addition to this improvement, a clear advantage was observed forthe CRAFT group only in the percentage of participants reaching the clinical threshold for meaningful change in untrained participation goals, which was more than double than the CCT and TAU groups (CRAFT-70% Vs. CCT-30% and TAU-20%). The significance of this finding is in line with Loh et al's (2016), expanding the international classification of functioning (ICF)'s concept of participation [48] by emphasizing the importance of targeting occupational- participation rather than focusing strictly on impaired body functions.

The improvement in the cognitive performance was found in only one (double decision) out of two tests that were directly trained during the intervention. The significant improvement in visual SOP that was observed in this study, is consistent with the evidence regarding the effectiveness of CCT for people with CRCI [44]. However, the visual working memory test (Bubble Pop) and auditory SOP (Sound Sweeps) did not show a similar improvement trend. Still, the improvement in just one of three cognitive domains found in this study could have in of itself contributed to the positive change on self-perception of improved cognitive function. This explanation is supported by recent findings, showing that cognitive training often results in improvements in perceived cognitive functioning even if improvements in actual cognitive performance are not evident [49, 50]. The treatment gain on objective and subjective cognitive measures are especially noteworthy considering the low dose (3 hours) of cognitive training set as a threshold, which has been previously found effective amongst people with depression [51], but is novel in the CRCI population. The improvement of the TAU group in subjective cognitive performance, albeit small, is noteworthy considering they didn't receive any intervention. This speaks to the importance of controlling for the effects of the assessment procedure itself, which may have therapeutic benefits [52].

In the pilot feasibility study of CRAFT [21], improvements were found in the social well-being subscale of the FACT-GP QoL questionnaire. An additional uncontrolled feasibility study implementing CO-OP in-person among individuals with CRCI found improvements in most of the subscales of the PROMIS questionnaire assessing HRQOL [25]. Similarly, A study implementing CCT among breast cancer survivors found a change in QoL in women an average of 5.5 years post cancer treatment [11, 53]. However, these findings of far transfer were not replicated in the current study. This may be due to limitation of the QoL tool used. Although the FACT-GP is widely used in studies of cancer survivors, a recent study found that a generic QoL instrument may be more suitable for identifying overall life satisfaction in long term survivors [54]. In addition, increased dosing of intervention components may contribute to improved QoL. Lastly, an additional confounding factor might be the outbreak of the

COVID-19 pandemic which occurred during the research phase and has a negative impact on QoL [55]. These findings warrant further investigation regarding the potential impact of CRAFT on QoL.

The dropout rates in the CRAFT group (20%) were as expected and were taken into consideration in sample size calculation, whilst the relatively high dropout in the CCT and TAU groups (CCT – 36%, TAU – 40%) are worthy of consideration. Interestingly, the COVID-19 pandemic did not increase the dropout rates in the CRAFT group but had an impact for the other groups. This difference might be explained by the therapeutic relationship developed during the CO-OP component of the CRAFT intervention, a key determinant of treatment outcomes [56], which outweighed the extreme conditions of the COVID-19 pandemic. Another important advantage in the CRAFT group was found on the treatment satisfaction questionnaire. Participants in the CRAFT group reported significantly higher levels of satisfaction with their treatment compared with the CCT group, especially considering the impact of the treatment on their daily life. Satisfaction has been suggested as a crucial factor in successfully transferring interventions into clinical practice [57] .These results suggest that application of CRAFT to people with CRCI may lead to alleviation of functional cognition problems.

The current study has several strengths and limitations. The design of this study is unique by comparing the target intervention with an active control group receiving an evidence-based treatment in addition to a no-contact control group. Secondly, the evaluation of clinical significance of treatment outcomes, beyond statistical significance, provides insight into the clinical value of the interventions, and promotes the translation of findings into practice. In addition, including a relatively diverse group of cancer survivors facing self-reported CRCI provides representation of this heterogeneous population and may support the generalization of findings to the real world. On the other hand, due to unexpected drop out rates in the CCT and TAU groups,, and low adherence to the CCT protocol, the final sample size was relatively small. Completing missing data was not possible due to large and uneven dropout rates between groups, so only completers were analysed. The sample available for the follow-up assessment was even smaller, limiting the conclusions pertaining to the stability of gains over time. In addition, the BrainHQ tests for measuring objective cognitive function were previously used among the CRCI population [44] however, it is relatively uncommon, limiting the comparison of these results to other similar studies. Finally, the treatment groups were not equal in terms of the number of hours they engaged in therapy which may have led to a bias in favour of the CRAFT group.

In conclusion, the current RCT demonstrates significant positive impact of CRAFT on cognitive and participation outcomes among individuals with CRCI. The CRAFT showed an advantage over CCT and TAU in terms of the percentage of participants achieving clinically meaningful change in occupational goals, lower attrition rates, and higher treatment satisfaction. Accordingly, the current findings suggest that patients with CRCI may benefit from a combination of cognitive training with occupation-based interventions .

Declarations

Ethical Approval

Ethical approval was obtained from Hadassah Helsinki committee Board on February 26, 2018 (protocol no. 0138-18-HMO)

Competing interests

The authors report no conflicts of interest.

Authors' contributions

Yafit Gilboa, Mor Nahum, Chen Makranz and were responsible for the study conception and design. Tamar Peretz and Talia Maeir applied for ethical approval. Talia Maeir, Ester Odem and Shani Tsabari were responsible for ongoing study procedure, participant recruitment, treatment, and data management. Talia Maeir was primarily responsible for data analysis and drafting the manuscript with support from Yafit Gilboa. All authors critically reviewed the manuscript for content and style and approved the final version of the manuscript for submission.

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Availability of data and materials

Data available on request from the authors

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Tables

Table 1. Sociodemographic and clinical characteristics of Study Participants				
	CRAFT (n=25)	CCT (n=25)	TAU (n=24)	*p*-value
Demographic Data				
Age, years mean±SD (range)	48.64±10.26 (23-68)	51.24±11.70 (25-73)	54.33±9.50 (33-69)	.175
Gender, n (%)				.368
Female	19 (76%)	21 (84%)	16 (66.7%)	
Male	6 (24%)	4 (16%)	8 (33.3%)	
Family status, n (%)				.088
Married	16 (64%)	21 (84%)	21 (87.5%)	
Single	3 (12%)	3 (12%)	2 (8.7%)	
Divorced	5 (20%)	0 (0%)	0 (0%)	
Widow	1 (4.3%)	1 (4.3%)	1 (4.3%)	
Years of education, mean±SD (range)	15.60±2.14 (12-18)	14.96±2.11 (12-18)	14.17±2.29 (11-20)	.084
Current employment status				.846
Not working (sick leave)	7 (29.2%)	10 (40%)	9 (37.5%)	
Part time	8 (33.3%)	6 (24%)	5 (20.8%)	
Full time	8 (33.3%)	6 (24%)	7 (29.2%)	
Retired	1 (4.2%)	3 (12%)	3 (12.5)	
Clinical Characteristics				
Cancer type, n (%)				.437
Breast	15 (60%)	15 (60%)	10 (41.7%)	
Colorectal	1 (4%)	5 (20%)	2 (8.3%)	
Lymphoma	4 (16%)	2 (8%)	2 (8.3%)	
Other	5 (20%)	3 (12%)	10 (41.7%)	
Months since therapy last treatment mean ±SD (range)	43.32±36.55 (6-135)	34.08±31.97 (9-148)	28.46±26.44 (6-109)	.265
Treatment modalities*, n (%)				
Chemotherapy	23 (92%)	25 (100%)	21 (87.5%)	.209
Surgery	21 (84%)	24 (96%)	20 (83.3%)	.307
Radiotherapy	16 (64%)	17 (68%)	14 (58.3%)	.780
Hormone therapy	7 (28%)	8 (32%)	2 (8.3%)	.110
MOCA	24.6±3.26 (19-30)	23.72±1.99 (21-27)	23.67±2.03 (19-28)	.344

PHQ-9	12.56±5.37 (3-21)	8.52±5.04 (2-21)	9.00±5.87 (0-19)	.021

Note. CRAFT cognitive retaining and functional treatment; CCT computerized cognitive training; TAU treatment as usual; SD standard deviation; MOCA Montreal cognitive assessment, score > 19 indicates no dementia. PHQ-9 patient health questionnaire, higher scores indicating more depressive symptoms.

*Most participants received more than one modality

Table 2. Study outcomes baseline-post intervention by group (n=38)

				CRAFT (n=14) Mean±SD	CCT (n=10) Mean±SD	TAU (n=14) Mean±SD	F interaction	η^2-
Participation in daily life	COPM – untrained goals	Performance	Baseline	3.73±1.94	4.40±1.04	5.19±1.47	5.31**	.238
			Post	6.26±2.38	5.72±1.86	5.58±1.00		
		Satisfaction	Baseline	2.91±1.47	3.20±1.01	4.47±1.77	6.34**	.272
			Post	6.13±2.52	5.52±2.49	5.41±1.57		
	FACTcog	Total	Baseline	53.79±19.73	63.70±22.02	77.13±23.81	4.90*	.224
			Post	78.73±24.71	89.03±22.44	83.71±19.48		
Cognitive performance	BrainHQ	Bubble Pop	Baseline	0.31±0.56	-0.85±0.52	-0.23±0.71	0.88	.058
			Post	1.06±1.79	0.19±0.74	0.18±0.80		
		Double Decision	Baseline	-1.24±0.87	-1.99±0.81	-1.93±0.96	5.68*	.289
			Post	-0.27±1.11	-0.13±1.26	-1.44±1.09		
		Sound Sweeps	Baseline	-2.98±1.41	-2.88±1.21	-3.01±1.29	0.27	.022
			Post	-2.04±1.49	-2.07±0.88	-1.91±1.26		
QoL	FACT - GP	Total	Baseline	43.57±9.56	52.60±16.69	58.95±14.19	0.97	.054
			Post	51.80±10.04	60.95±12.19	60.20±18.30		

Note. CRAFT cognitive retaining and functional treatment; CCT computerized cognitive training; TAU treatment as usual; SD standard deviation; COPM Canadian occupational performance measure. FACTcog FACT cognitive; FACT GP Fact general practice. η^2 = 0.01 indicates a small effect; η^2 = 0.06 indicates a medium effect; η^2 = 0.14 indicates a large effect.

Table 3. Study outcomes post-intervention - follow up by group (n=32)					
			CRAFT (n=12)	CCT (n=10)	TAU (n=10)
			Mean±SD	Mean±SD	Mean±SD
COPM – untrained goals	Performance	post	6.04±2.47	5.72±1.86	5.51±1.12
		FU	6.20±2.32	5.67±1.99	5.17±1.43
	Satisfaction	post	5.87±2.69	5.52±2.49	5.36±1.57
		FU	6.23±2.51	5.78±1.96	5.79±1.36
FACTcog	Total	post	79.31±26.38	89.03±22.44	83.60±18.82
		FU	79.58±25.55	85.32±29.05	85.63±20.87
BrainHQ	Bubble pop	post	1.10±1.88	0.12±0.74	0.15±0.81
		FU	0.62±0.46	0.27±0.82	-0.08±0.61
	Double decision	post	-0.17±1.16	0.18±1.28	-1.29±0.87
		FU	-0.22±1.14	-0.36±1.21	-0.93±1.07
	Sound sweeps	post	-1.77±1.41	-1.85±0.69	-1.91±1.34
		FU	-1.70±1.22	-1.40±0.57	-2.37±1.25
FactGP	Total	post	50.77±10.32	60.95±12.19	59.15±20.39
		FU	49.48±15.16	57.39±16.28	60.47±15.89
Note. CRAFT cognitive retaining and functional treatment; CCT computerized cognitive training; TAU treatment as usual; FU follow up; SD standard deviation; COPM Canadian occupational performance measure. FACTcog FACT cognitive; FACT GP Fact general practice.					

Figures

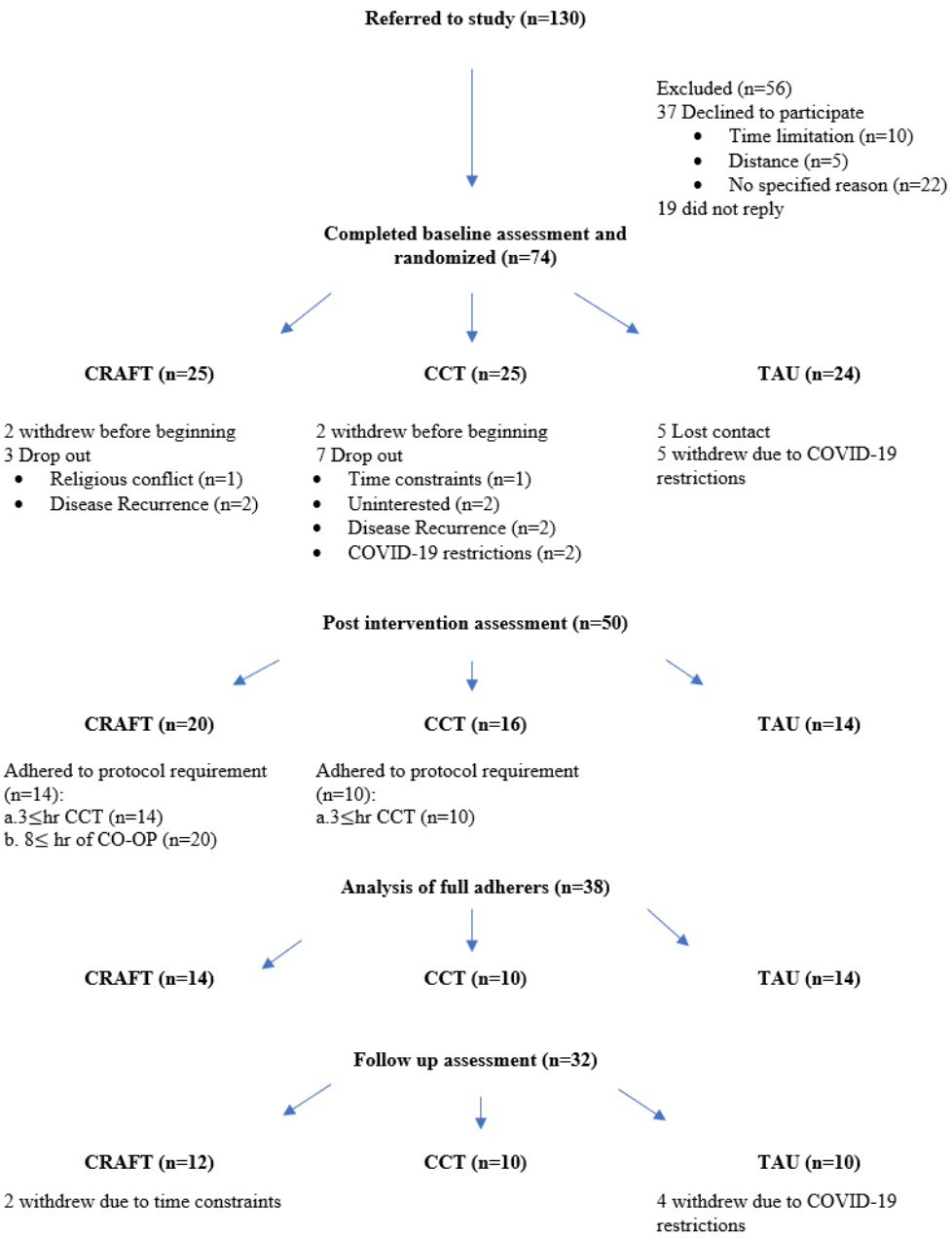

Figure 1

Study flow

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